

29th September, 1965.

Dr. Jacques Monod,  
Institut Pasteur,  
25 Rue du Docteur Roux,  
Paris XV, FRANCE.

Dear Jacques,

We have now understood your footnote (page 115) ("the essence of the paper") and in our view it is grossly misleading, almost to the point of being false. Your error is that in comparing the tetramer with the monomer you took  $L = 1000$  for both. This is cheating. To make a fair comparison you should take  $L$  for the monomer as 1000. This is because if the free energy difference between the R and the T state for the monomer is  $E_0$ , then for the tetramer it is only fair to take it as  $4E_0$ . We have assumed a model in which the protomers in the tetramer are rigidly coupled together so that the tetramer is all T or all R, as required by your theoretical treatment, but that otherwise the protomers do not interact.

It is thus easy to show that, whatever the value of  $c$  (you merely considered the special case  $c = 0$ ) the value of  $\alpha$  which makes  $\frac{ET}{ER} = 1$  is identical for the monomer or the tetramer. For the case you considered ( $\frac{ET}{ER} = 0.1$ ) and  $c = 0$  there is a small advantage:  $\alpha$  for the monomer would have to be about 55 instead of 9 - a factor of 6, not a factor of thousands.

I have set out all this in a short note for J. Mol. Biol., a copy of which I enclose. As you can see from this there are indeed cases where an oligomer is much better than a monomer, but these depend on the sigmoid nature of the binding curves.

Do let me know what you think about this. I'm sending a copy of both this letter and the note to Jeffries.

F. H. C. Crick

c.c. Dr. J. Wyman